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Retrograde Coronary Venous Administration of Recombinant Tissue-Type Plasminogen Activator: A Unique and Effective Approach to Coronary Artery Thrombolysis

AKIRA MIYAZAKI, MD,* HIROYUKI TADOKORO, MD, J. KEVIN DRURY, MD, FACC, LARS RYDÉN, MD, FACC, ROBERTO V. HAENDCHEN, MD, ELIOT CORDAY, MD, FACC

Los Angeles, California

Recent studies of interventional therapy by way of the coronary venous system have demonstrated that it can protect acutely ischemic myocardium. To evaluate the efficacy of coronary venous retroinfusion compared with systemic intravenous administration of recombinant tissue-type plasminogen activator (rt-PA), 14 dogs were studied with a copper coil-induced thrombus in the left anterior descending coronary artery. The rt-PA (24,000 fluorescence units/kg) was administered continuously, either intravenously (n = 8) or retrogradely (n = 6), for 30 min beginning 60 min after coronary occlusion. Thrombolysis was determined by repetitive coronary angiography. All dogs were killed 3 h after termination of rt-PA infusion and infarct size was measured by the triphenyltetrazolium chloride staining technique.

Complete thrombolysis occurred in five of the six dogs in the retroinfusion group and four of the eight dogs in the systemic intravenous infusion group. Partial lysis was achieved in two dogs treated by intravenous infusion. Lysis did not occur in one dog treated with retroinfusion and in two dogs treated with intravenous infusion. Time to thrombolysis was 13.4 ± 2.3 min in the retroinfusion group versus 27.8 ± 4.8 min in the intravenous group ($p < 0.001$). Myocardial functional recovery in the ischemic zone measured by two-dimensional echocardiography 60 min after reperfusion was significant only in the retroinfusion group ($p < 0.05$). Infarct size expressed as a percent of the risk area (autoradiography) was significantly smaller in the retroinfusion group (34.9 ± 11.9%) than in the intravenous group (54.5 ± 19.1%; $p < 0.05$) despite <15 min difference in average ischemic time between the groups (73.4 vs. 87.8 min). It is speculated that retroinfusion of rt-PA may prevent downstream embolization of microthrombi. No myocardial hemorrhages or damage to the coronary venous system were observed.

It is concluded that coronary venous retroinfusion of rt-PA provides more rapid clot lysis and better functional recovery and infarct size reduction compared with systemic intravenous administration.

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Various new therapeutic techniques for acute myocardial infarction have been developed in the past 2 decades. Experimental (1–3) and more recently clinical (4–9) studies have indicated that early and adequate restoration of coronary blood flow after acute myocardial infarction can reduce infarct size and improve myocardial function. Large randomized clinical trials (10–13) have also demonstrated that early coronary thrombolysis reduces the mortality rate in patients with acute myocardial infarction. Streptokinase has been commonly used in thrombolytic therapy administered by an intracoronary (5,6,13) or intravenous (10–12) route; however, the results have not been fully satisfactory (14). More recently, new fibrin-specific thrombolytic agents such as recombinant tissue-type plasminogen activator (rt-PA) have been applied in clinical studies (15–19).

Interventions by way of the coronary sinus have been extensively studied (20) as an alternative route for delivery of oxygenated blood and drugs into the jeopardized myocardium during coronary artery occlusion. Beneficial effects of synchronized retroperfusion (21–27) and retroinfusion (28–31) of drugs on ischemic myocardium have been clearly demonstrated in experimental studies. We (32) previously showed that coronary venous retroinfusion of streptokinase was associated with more rapid clot lysis compared with systemic intravenous infusion in a model of acute coronary artery occlusion.

The purpose of this study was to compare the efficacy of retrograde administration of rt-PA into the great cardiac vein with that of systemic infusion in the setting of a thrombus-induced acute coronary artery occlusion, with respect to

From the Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center and the University of California, Los Angeles, School of Medicine, Los Angeles, California. This study was supported in part by Grants HL 14644-14 and HL 17651-14 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; the Medallion Group of Cedars-Sinai Medical Center, the Schreiber Family Foundation, the Wallis Foundation, the Feintech Family Foundation, Geri and Richard Brawerman and Mrs. Theodore Cummings, Los Angeles.

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*Current address: Akira Miyazaki, MD, The 3rd Department of Internal Medicine, School of Medicine, Chiba University, 1-8 Inohana, Chiba City, Japan.

Address for reprints: Eliot Corday, MD, Cedars-Sinai Medical Center, Halper Building, Room 325, 8700 Beverly Boulevard, Los Angeles, California 90048.

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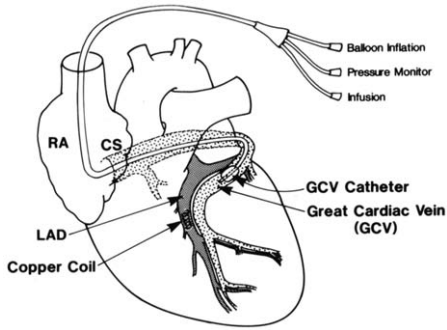

Figure 1. Scheme of the experimental preparation. A copper coil is positioned in the proximal left anterior descending coronary artery (LAD) to induce thrombus formation. A 5F triple lumen balloon-tipped catheter is introduced into the great cardiac vein (GCV) for regional coronary venous occlusion, drug administration and coronary venous pressure monitoring. CS = coronary sinus; RA = right atrium.

rapidity of lysis as well as early myocardial functional recovery and ultimate infarct size.

Methods

Experimental preparation. Sixteen male or female mongrel dogs, weighing 20 to 35 kg, were premedicated with morphine sulfate (1 mg/kg body weight intramuscularly) and anesthetized with sodium thiopental (25 mg/kg intravenously). After tracheal intubation, respiration was controlled with a semiclosed circuit Harvard respirator. Respiration volume and rate were adjusted to maintain arterial pH and partial pressure of carbon dioxide (Pco_2) within the physiologic range (pH 7.35 to 7.45; Pco_2 35 to 45 mm Hg). Anesthesia was maintained with a mixture of enflurane and oxygen.

A 7F venous catheter was inserted into the inferior vena cava for intravenous administration of saline solution and rt-PA solution. Aortic and pigtail catheters were introduced through the femoral artery into the ascending aorta and left ventricle, respectively, and connected to a Statham P23Db transducer. In all dogs, a 5F triple-lumen balloon-tipped retroinfusion catheter (Retroinfusion Systems) was introduced into the coronary sinus through the left jugular vein and advanced to the great cardiac vein under fluoroscopic guidance (Fig. 1). Two of these lumens opened at the end of the catheter tip and were used for pressure monitoring and drug infusion. Another lumen opened into the balloon for occlusion of the coronary sinus and compartmentalization of the coronary veins to enhance drug delivery into the ischemic myocardium.

A copper coil-induced thrombus technique was used for the coronary artery occlusion (33). After inserting a 7F angiographic catheter from the left carotid artery into the ostium of the left anterior descending coronary artery, a straight guide wire (0.035 in. [0.089 cm] diameter) was inserted 5 to 7 cm into the coronary artery through the angiographic catheter under fluoroscopic guidance. The catheter was then withdrawn from the carotid artery. A 25 gauge copper wire coil (10 to 12 mm in length, 2 to 3 mm in outer diameter) was placed over the guide wire and advanced by the 7F catheter 2 to 3 cm into the proximal left anterior descending artery. After withdrawal of the intracoronary guide wire, the angiographic catheter was drawn into the aortic root for later coronary angiography. Until total heparinization was achieved, all catheter lumens were continuously flushed with saline solution at a low flow rate to prevent clot occlusion.

Measurements. The electrocardiogram (ECG) and all pressures were continuously monitored on an Electronics for Medicine V-12 physiologic recorder. The left ventricular short-axis view recorded with two-dimensional echocardiography (Advanced Technology Laboratories, model MK300LX) was employed to measure myocardial systolic function in the ischemic region. Short-axis views at the low papillary muscle level were subdivided into eight equally spaced segments, using a standardized fixed axis with an internal referencing system (23).

Percent systolic fractional area change (%FAC) was calculated by the following formula: %FAC = [(EDA − ESA)/EDA] × 100, where EDA = end-diastolic area and ESA = end-systolic area. These variables were calculated and obtained with use of a computer-assisted system as previously described (23) by an observer who did not know the angiographic and pathologic results. The ischemic segment was defined as the segment that had the most depressed systolic fractional area change during coronary occlusion.

Experimental protocol. The ST segment elevation on the ECG and anteroseptal wall motion abnormality on the two-dimensional echocardiogram were used for confirmation of ischemia in the distribution of the left anterior descending coronary artery. Coronary angiography was then performed to confirm the coronary occlusion.

Before initiation of thrombolytic therapy, heparin

(100 IU/kg) was administered to prevent rethrombosis at the coil during and after thrombolytic therapy and subsequently supplemented by 50 IU/kg intravenously every hour. The dogs were then randomly assigned to one of the two treatment groups.

Intravenous infusion group. After 60 min of occlusion, human melanoma single chain rt-PA (24,000 fluorescence units/kg [≅0.2 mg/kg] [Bio-Response, Inc.] dissolved into 240 ml of saline solution) was continuously infused over 30 min into the inferior vena cava.

Coronary sinus retroinfusion group. The same amount of rt-PA was continuously infused over 30 min through the lumen of the retroinfusion catheter into the great cardiac vein. If the mean great cardiac vein pressure was <20 mm Hg, additional saline solution was retroinfused simultaneously to maintain the pressure at >20 mm Hg with use of a Harvard peristaltic pump (model 500-1200). When the mean great cardiac vein pressure was >40 mm Hg or the peak pressure was >60 mm Hg, the rate of infusion of additional saline solution was reduced or the balloon of the retroinfusion catheter was deflated, or both, to reduce the pressure. After recanalization, the catheter balloon was deflated and additional infusion of saline solution was abandoned to prevent coronary venous damage by excessively high coronary venous pressure.

To detect recanalization of the coronary artery, repetitive angiography was performed at 5 min intervals (or immediately if significant reperfusion arrhythmias [accelerated idioventricular rhythm or frequent premature ventricular beats] occurred). To avoid manual transmission of hydrostatic force and high intracoronary arterial pressure during angiography, the angiographic catheter tip was narrowed and never wedged into the coronary artery. Reperfusion was defined by the criteria described in the Thrombolysis in Myocardial Infarction (TIMI) trial (9). Administration of rt-PA was continued for 30 min to complete the drug infusion protocol, even if recanalization had already occurred. After recanalization was confirmed, coronary angiography was repeated at 5 and 10 min after reperfusion to confirm sustained patency.

Hemodynamic and two-dimensional echocardiographic data were obtained before coronary occlusion, after 1 h of occlusion and then at 20 min and 1, 2 and 3 h after rt-PA infusion. Three hours after completion of rt-PA administration, the dogs were killed with an overdose of potassium chloride.

Pathologic study. Autoradiography was used to detect the perfusion area with a bolus injection of 10 mCi of technetium-99m–labeled albumin microspheres (3M Instant Microspheres, mean diameter 20 μm) into the left ventricle 60 min after coronary occlusion (34). After induced death, the heart was removed and the left ventricle was sliced into 5 to 7 mm thick transverse sections parallel to the atrioventricular groove. These slices were incubated in triphenyltetrazolium chloride solution for 30 min to define the area of necrosis (represented by the unstained area) (35). Epicardial and endocardial outlines as well as areas of necrosis were traced on transparent sheets. The slices were then laid on an X-ray film for 12 h. The exposed area by gamma-rays from technetium-99m microspheres represented the perfusion (nonischemic) area. The exposed areas and outlines of cross sections of the slices were traced on the same sheet; therefore, ischemic areas were represented by the unexposed areas on the sheet. The size of the ischemic and infarct areas was quantified by planimetry and expressed as a percent of the total cross-sectional area of all slices and as the ratio of infarct to ischemic area. The coronary sinus and coronary veins were also examined for damage from retroinfusion and residual clots on the copper coil were examined.

Statistical analysis. The time of thrombolysis and infarct size in the two groups were statistically analyzed by Student's *t* test. Hemodynamic and two-dimensional echocardiographic data were analyzed by a repeated measure analysis of variance. When this analysis indicated intergroup differences at one or more measurement times, the times when differences occurred were further evaluated with Scheffé's *t* test.

Table 1. Thrombolysis in the Intravenous (n = 8) and Coronary Venous Retroinfusion (n = 6) Groups

Thrombolysis Outcome	No. of Dogs	Lysis Time (min)
Intravenous infusion group		
Successful thrombolysis	6 (full = 4; partial = 2)	27.8 ± 4.8
Unsuccessful thrombolysis	2	—
Retroinfusion group		
Successful thrombolysis	5 (full = 5; partial = 0)	13.4 ± 2.3*
Unsuccessful thrombolysis	1	—

*$p < 0.001$ versus time in intravenous infusion group. Values are mean values ± SD. full = full reperfusion; partial = partial reperfusion.

Results

Two dogs died before randomization and were excluded from the study.

Thrombolysis (Table 1). Intravenous infusion of rt-PA resulted in thrombolysis in six of the eight dogs. Full reperfusion (TIMI grade 3), however, occurred in only four of these dogs. In the retroinfusion group, thrombolysis occurred in five of the six dogs and full reperfusion (TIMI grade 3) occurred in all five dogs. Time to thrombolysis (including dogs with partial lysis) was more rapid in the retroinfusion group (13.4 ± 2.3 min) than in the intravenous infusion group (27.8 ± 4.8 min; $p < 0.001$). There were no clots at the site of the copper coil after induced death in any dogs that showed full recanalization on arteriography.

Hemodynamics (Table 2). There was no statistically significant difference in heart rate, mean aortic pressure, left ventricular end-diastolic pressure or its first derivative (dP/dt) between the two groups during the entire experimental period.

Table 2. Hemodynamic Data From the Intravenous Infusion Group (n = 6) and Coronary Venous Retroinfusion Group (n = 4)*

	Before Occlusion	1 Hour of Occlusion	After Reperfusion (min)			
			30	60	120	180
Heart rate (beats/min)						
Intravenous infusion	65 ± 12	90 ± 17	106 ± 33	94 ± 19	96 ± 20	100 ± 22
Coronary venous retroinfusion	62 ± 17	92 ± 28	116 ± 30	93 ± 9	120 ± 25	96 ± 22
Mean aortic pressure (mm Hg)						
Intravenous infusion	85 ± 7	78 ± 25	79 ± 23	75 ± 21	67 ± 16	65 ± 12
Coronary venous retroinfusion	84 ± 9	73 ± 21	72 ± 29	74 ± 18	67 ± 15	66 ± 10
LVEDP (mm Hg)						
Intravenous infusion	3 ± 2	9 ± 4	7 ± 7	5 ± 3	6 ± 2	6 ± 2
Coronary venous retroinfusion	3 ± 1	8 ± 3	7 ± 4	6 ± 4	6 ± 2	4 ± 2
LV dP/dt (mm Hg/s × 10^3)						
Intravenous infusion	1.6 ± 0.5	1.1 ± 0.2	1.0 ± 0.4	1.0 ± 0.3	0.8 ± 0.3	0.8 ± 0.2
Coronary venous retroinfusion	1.9 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	1.1 ± 0.1	1.0 ± 0.2	0.9 ± 0.1

*Dogs without thrombolysis are excluded. Data from one dog in the coronary venous retroinfusion group are missing. dP/dt = first derivative of left ventricular pressure. Values are mean ± SD. LV = left ventricular; LVEDP = left ventricular end-diastolic pressure.

Infarct size (Fig. 2). Area at risk expressed as a percent of left ventricle was approximately 35% in both groups. Infarct size was significantly smaller in the dogs in which rt-PA was administered into the coronary vein (8.6 ± 6.3%) than in those receiving systemic intravenous infusion (18.7 ± 6.8%; $p < 0.05$). Infarct size expressed as a percent of the risk area was also significantly smaller in the coronary venous retroinfusion group (34.9 ± 11.9%) than in the intravenous infusion group (54.5 ± 19.1%; $p < 0.05$).

Two-dimensional echocardiography (Fig. 3). After coronary artery occlusion, regional myocardial function expressed as ischemic zone systolic fractional area change

Figure 2. Graphic representation of left ventricular (LV) area at risk and infarct size expressed as a percent of left ventricle in the intravenous infusion group (**open bars**, n = 6) and the coronary venous retroinfusion group (**shaded bars**, n = 5) (mean values ± SD). Also shown is infarct area expressed as a percent of the area at risk. Infarct size was significantly smaller after coronary venous retroinfusion of recombinant tissue-type plasminogen activator than after systemic intravenous infusion. These data include only dogs in which lysis was achieved. *$p < 0.05$ versus intravenous infusion.

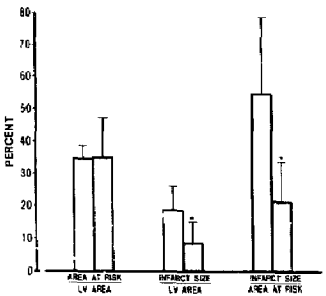

Figure 3. Regional ischemic myocardial function expressed as percent systolic fractional area change (FAC) in the intravenous infusion group (**open bars**, n = 7 before reperfusion; n = 6 after reperfusion) and the coronary venous retroinfusion group (**shaded bars**, n = 5 before reperfusion; n = 4 after reperfusion). Thrombotic occlusion of the left anterior descending coronary artery resulted in akinesia in the ischemic zone. Ischemic zone function improved with coronary venous retroinfusion of recombinant tissue-type plasminogen activator, but not by the systemic intravenous administration route. Data from one dog in each group are missing. *$p < 0.05$ versus intravenous infusion.

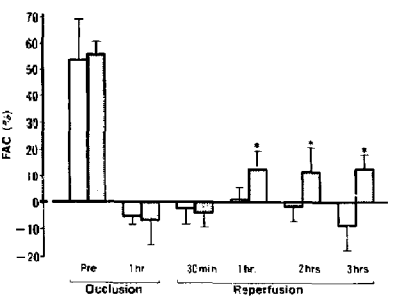

Table 3. Coronary Venous Pressure in the Intravenous Infusion Group and Coronary Venous Retroinfusion Groups

	Before Infusion (mm Hg)	During Infusion (mm Hg)	After Infusion (mm Hg)
Intravenous group (n = 7)			
Maximum	9.0 ± 1.0	10.7 ± 1.2	6.0 ± 3.5
Minimum	2.7 ± 3.1	5.3 ± 4.6	3.3 ± 3.1
Mean	5.0 ± 1.7	7.0 ± 3.0	4.7 ± 3.2
Retroinfusion group (n = 5)			
Maximum	9.3 ± 3.8	41.2 ± 5.8	5.4 ± 4.1
Minimum	1.8 ± 2.5	11.6 ± 4.8	0.8 ± 1.8
Mean	4.2 ± 2.9	24.4 ± 4.8	3.0 ± 2.9

Data are presented as mean values ± SD. Data from one dog in each group are missing. Abbreviations as in Table 1.

demonstrated severe dyskinesia in both groups. After reperfusion, ischemic zone function improved in dogs receiving coronary venous rt-PA retroinfusion; however, these values remained at the hypokinetic level. Conversely, regional ischemic zone function in dogs receiving systemic intravenous infusion showed only transient minor recovery, returning to dyskinesia after 2 h of reperfusion. The differences between groups were statistically significant after 60 min of reperfusion ($p < 0.05$).

In the retroinfusion group, there was a strong inverse correlation ($r = -0.89$) between infarct size expressed as a percent of area at risk and ischemic zone function at 3 h after reperfusion. In the intravenous infusion group, however, there was no such correlation.

Retroinfusion and the coronary veins (Table 3). Retroinfusion was performed during continuous coronary venous pressure monitoring. Coronary venous pressure was low before retroinfusion and the peak pressure increased to 41.2 ± 5.8 mm Hg during retroinfusion. Minimal pressure was 11.6 ± 4.8 mm Hg and mean pressure reached 24.4 ± 4.8 mm Hg. After completion of the retroinfusion, coronary venous pressure returned to baseline values.

The coronary veins were inspected after the animals' death. There was a small hematoma around the coronary sinus and slight endothelial erosion of the great cardiac vein in one dog. There was no significant damage to the coronary veins in any dogs in the retroinfusion group.

Discussion

Regional coronary venous administration of rt-PA resulted in more rapid thrombolysis, earlier recovery of regional myocardial function and a greater reduction in infarct size compared with intravenous administration.

Previous studies on retroperfusion. Synchronized retroperfusion with streptokinase for experimental coronary thrombolysis was previously demonstrated by Meerbaum et al. (32). In that study, thrombolysis occurred more rapidly in the retroperfusion group (51 ± 13 min) than in the systemic intravenous infusion group (132 ± 61 min), even though the doses of streptokinase were <20% of the amount currently recommended for intravenous administration in patients with acute myocardial infarction. We (36) previously showed more rapid thrombolysis, earlier myocardial functional recovery and smaller infarct size using retrograde administration of streptokinase into the great cardiac vein without synchronized retroperfusion of arterial blood in dogs. Because of differences in experimental design, it is difficult to compare the time to thrombolysis between these two studies. However, from previous reports, it can be stated that retrograde administration of streptokinase with or without synchronized retroperfusion reduces the time to thrombolysis to <50% of that with systemic administration.

Gold et al. (37) reported that the time to thrombolysis after intravenous administration of rt-PA was dose dependent in an experimental study of coronary thrombolysis with thrombin-induced thrombosis. Clinical studies (15,19) have also shown dose-dependent thrombolysis after intravenous administration of rt-PA. Other studies (15,17) reported that reperfusion occurred in approximately 70% of patients receiving 80 to 100 mg of rt-PA, whereas more recent studies (18,19) have shown a recanalization rate of approximately 80% with doses of 1.25 mg/kg or 150 mg and a linear trend between the dose and the rate of success of thrombolysis (18,19). Therefore, rapid thrombolysis and high recanalization rates may be dependent on high concentrations of the drug in plasma and at the site of the thrombus.

Coronary venous retroinfusion of several pharmacologic agents has demonstrated that this technique is associated with high myocardial drug concentrations in the ischemic tissue (29,38), similar to the concentrations achieved by direct coronary artery infusion (39). Furthermore, studies of coronary venous retroperfusion of arterial blood (21) and drug retroinfusion (29,38,39) have demonstrated transcapillary delivery from the venous to the arterial side. Administration of a thrombolytic agent into the coronary vein may reach the arterial thrombus directly through capillaries and from larger venoarterial shunts as well as systemically. Therefore, retroinfusion of a thromoolytic agent has the potential to lyse the clot from both the proximal and the

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distal sides of the thrombus, which may explain the more effective and more rapid thrombolysis observed in our study, whereas thrombolytic agents administered systemically are diluted in a large blood pool and can lyse the thrombus only from the proximal arterial side.

Infarct size and myocardial function. This study also shows smaller infarct size and better myocardial functional recovery after retroinfusion than after systemic intravenous infusion of rt-PA. The primary reason could be related to the shorter period of ischemia in the retroinfusion group (73.4 ± 2.3 min) than in the systemic intravenous group (87.8 ± 4.8 min). However, the average time difference from coronary occlusion to thrombolysis between the two groups was only about 15 min, which is probably too short to explain the relatively large difference in infarct size (34.9 ± 11.9% vs. 54.5 ± 19.1%). This result suggests that retroinfusion may lyse small thrombi or prevent microembolization in the peripheral vascular bed distal to the occluded epicardial coronary artery.

Even after short periods of ischemia, complete myocardial functional recovery may be delayed for ≥24 h (40,41). It has been reported (42) that the pattern of reflow after thrombolysis is unstable and intermittent. In the present study, despite a relatively prolonged ischemic time, myocardial functional recovery in the ischemic zone after reperfusion was significantly faster in the retroinfusion compared with the intravenous infusion group ($p < 0.05$). Moreover, this phenomenon was strongly related to the size of the infarct. We believe that the lack of improvement in regional function in the intravenous infusion group is related to the larger infarcts in that group, even though we cannot rule out the possible detrimental effect of thrombus debri in the microcirculation or the possibility of delayed functional recovery had we extended the period of observation after reperfusion. In the intravenous infusion group, even in the dog with the smallest infarct (infarct size/area at risk 24.5%, time to lysis 27 min), there was severe dyskinesia in the ischemic zone (area change −11.4%) at 3 h of reperfusion. Therefore, from these data, it is suggested that retroinfusion of rt-PA enhances the actual or effective reperfusion in the microvascular bed, resulting in a shorter period of severe ischemia.

Coronary venous involvement. In the present study, coronary venous pressure was continuously monitored during the retrograde infusion because it has been shown (21,22,25,43) that high coronary venous pressure (mean pressure >40 mm Hg or peak pressure >60 mm Hg) may cause intramyocardial bleeding, edema or venule damage. In our study, mean coronary venous pressure was maintained at approximately 20 mm Hg to achieve and enhance effective retrograde drug delivery. A previous study (44) also demonstrated a close relation between coronary venous pressure during retroinfusion and the resulting ischemic myocardial perfusion. In our study, all dogs in the retroinfusion group were examined after death and there was no serious damage in the great cardiac vein where the coronary venous occlusion was carried out. In a recent preliminary clinical study (45), it was demonstrated that catheterization of the coronary sinus can be easily performed in humans with a percutaneous approach and that retroperfusion is safe.

Study limitations. In the present study, although a coronary sinus catheter was placed in both groups of dogs, temporary coronary sinus occlusion was carried out only in the coronary venous retroinfusion group. This is important because some investigators (46) have previously reported significant infarct size reduction with intermittent coronary sinus occlusion, although this has not been confirmed by others (47). However, the coronary venous retroinfusion group had only a single (and not intermittent) coronary sinus occlusion, which to our knowledge has not been reported to reduce infarct size. In fact, prolonged coronary sinus occlusion is associated with a slight reduction in epicardial coronary artery blood flow (48). Intermittent coronary sinus occlusion, however, should not be confused with pressure-controlled intermittent coronary sinus occlusion, which has been more consistently associated with infarct size reduction in experimental studies (49).

Another limitation of our study was the lack of a bolus infusion of rt-PA. In current clinical practice in patients with acute myocardial infarction, rt-PA is usually given as a bolus infusion (10% of the total dose) followed by a 3 h continuous infusion. Although we did not give an initial bolus infusion, the total dose of rt-PA was given in only 30 min in our study as opposed to the 3 h administration in clinical practice.

Clinical implications. In clinical practice, thrombolysis is an established and commonly used procedure for patients with acute myocardial infarction, with reported (15–19) recanalization rates of 60% to 75% with intravenous administration of rt-PA. However, in the remaining 25% to 40% of patients with unsuccessful thrombolytic recanalization, failure may be due to the delay in starting administration or the less efficacious intravenous administration, or both. Recent trials (50) employed larger intravenous doses than those used earlier to enhance effective recanalization rates. Although this practice increases the success rate, it also increases the chance of severe accidental bleeding.

This study shows that coronary venous retroinfusion of small doses of rt-PA provides more rapid thrombolysis and more effective reperfusion than does systemic infusion. Early thrombolysis was achieved using only 15% to 20% of the intravenous rt-PA doses currently used in patients with acute myocardial infarction. This effect may be due to a higher concentration of the drug around the thrombus. Earlier thrombolysis was associated with improved ischemic zone myocardial function after reperfusion and infarct size was also significantly reduced in dogs receiving rt-PA by way of the coronary vein compared with that after systemic infusion. This difference could not be explained on the basis of a small difference in ischemic time between the two groups. It is therefore speculated that retroinfusion of rt-PA may actually prevent embolization of microthrombi to the microcirculation.

It is also possible to combine retroinfusion of thrombolytic agents with retroinfusion of drugs that have the potential to reduce reperfusion injury or reperfusion arrhythmias, or both (14–16). Indeed, previous studies from our laboratory (30,31,38) and others (28,51) comparing retroinfusion with systemic drug infusion during acute coronary occlusion have demonstrated not only increased myocardial drug concentration, but also enhanced efficacy of infarct-reducing agents infused through the coronary veins, particularly when these drugs are administered before reperfusion. Thus, retroinfusion of thrombolytic agents can be used as an alternative or adjunct method to systemic thrombolysis. Investigation of the use of this technique in patients with acute myocardial infarction may be justified.

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References

1. Maroko PR, Libby P, Ginks WR, et al. Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. J Clin Invest 1972;51:2710–6.
2. Costantini C, Corday E, Lang TW, et al. Revascularization after 3 hours of coronary arterial occlusion: effects on regional cardiac metabolic function and infarct size. Am J Cardiol 1975;36:368–84.
3. Kloner RA, Ellis SG, Lange R, Braunwald E. Studies of experimental coronary artery reperfusion: effects on infarct size, myocardial function, biochemistry, ultrastructure and microvascular damage. Circulation 1983; 68(Suppl I):I-8–15.
4. Rentrop P, Blanke H, Karsch KR, et al. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. Circulation 1981;62:307–17.
5. Ganz W, Buchbinder N, Marcus H, et al. Coronary thrombolysis in evolving myocardial infarction. Am Heart J 1981;101:4–13.
6. Richie JC, Davis KB, Williams DC, et al. Global and regional left ventricular function and tomographic radionuclide perfusion: the Western Washington Intracoronary Streptokinase in Myocardial Infarction Trial. Circulation 1984;70:867–75.
7. Serruys PW, Simoons ML, Suryapranata H, et al. Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. J Am Coll Cardiol 1986;7:729–42.
8. Simoons ML, Serruys PW, van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986;7:717–28.
9. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987;317:850–5.
10. Gruppo Italiano per lo Studio Della Streptochinasi nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–403.
11. ISAM study group. A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM): mortality, morbidity, and infarct size at 21 days. N Engl J Med 1986;314:1465–71.
12. ISIS-2 (Second International Study of Infarct Survival) collaborative group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction. Lancet 1988;2:349–60.
13. Kennedy JW, Ritchie JL, Davis KB, et al. The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12 month follow-up report. N Engl J Med 1985;312:1073–8.
14. Selzer A. Does thrombolytic therapy reduce infarct size? J Am Coll Cardiol 1989;13:1431–4.
15. Verstraete M, Bory M, Collen D, et al. Randomised trial of intravenous recombinant tissue-plasminogen activator versus intravenous streptokinase in acute myocardial infarction: report from the European Cooperative Study Group for recombinant tissue-type plasminogen activator. Lancet 1985;1:842–7.
16. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932–6.
17. Collen D, Topol EJ, Tiefenbrunn AJ, et al. Coronary thrombolysis with recombinant human tissue-type plasminogen activator: a prospective randomized placebo-controlled trial. Circulation 1984;70:1012–7.
18. Topol EJ, Morris DC, Smalling RW, et al. A multicenter, randomized, placebo-controlled trial of a new form of intravenous recombinant tissue-type plasminogen activator (Activase) in acute myocardial infarction. J Am Coll Cardiol 1987;9:1205–13.
19. Mueller HS, Rao AK, Forman SA, and the TIMI Investigators. Thrombolysis in myocardial infarction (TIMI): comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator. J Am Coll Cardiol 1987;10:479–90.
20. Corday E, Meerbaum S, Drury JK. The coronary sinus: an alternate channel for administration of arterial blood and pharmacologic agents for protection and treatment of acute cardiac ischemia. J Am Coll Cardiol 1986;7:711–4.
21. Meerbaum S, Lang TW, Osher JV, et al. Diastolic retroperfusion of acutely ischemic myocardium. Am J Cardiol 1976;37:588–98.
22. Farcot JC, Meerbaum S, Lang TW, et al. Synchronized retroperfusion of coronary veins for circulatory support of jeopardized ischemic myocardium. Am J Cardiol 1978;21:1194–202.
23. Feerdchen RV, Corday E, Meerbaum S, Povshitkov M, Rit J, Fishbein MC. Prevention of ischemic injury and early reperfusion derangements by hypothermic retroperfusion. J Am Coll Cardiol 1983;1:1067–80.
24. Yamazaki S, Drury JK, Meerbaum S, Corday E. Synchronized coronary venous retroperfusion: prompt improvement of left ventricular function in experimental myocardial ischemia. J Am Coll Cardiol 1985;5:655–63.
25. Povshitkov M, Haendchen RV, Meerbaum S, Fishbein MC, Shell W, Corday E. Prostaglandin E, coronary venous retroperfusion in acute myocardial ischemia: effects on regional left ventricular function and infarct size. J Am Coll Cardiol 1984;3:939–47.
26. Drury JK, Yamazaki S, Fishbein MC, Meerbaum S, Corday E. Synchronized diastolic coronary venous retroperfusion: results of a preclinical safety and efficacy study. J Am Coll Cardiol 1985;6:328–35.
27. Chang B-L, Drury JK, Meerbaum S, Fishbein MC, Whiting J, Corday E. Enhanced myocardial washout and retrograde blood delivery with synchronized retroperfusion during acute myocardial ischemia. J Am Coll Cardiol 1987;9:1093–8.
28. Smith GT, Geary GG, Blanchard W, McNamara JJ. Reduction in infarct size by synchronized selective coronary venous retroperfusion of arterialized blood. Am J Cardiol 1981;48:1064–70.
29. Karagueuzian HS, Ohta M, Drury JK, et al. Coronary venous retroinfusion of procainamide: a new approach for the management of spontaneous and inducible sustained ventricular tachycardia during myocardial infarction. J Am Coll Cardiol 1986;7:551–61.
30. Hatori N, Miyazaki A, Tadokoro H, et al. Beneficial effects of coronary venous retroinfusion of superoxide dismutase and catalase on reperfusion arrhythmias, myocardial function and infarct size in dogs. J Cardiovasc Pharmacol. 1989;14:396–404.
31. Hatori N, Tadokoro H, Satomura K, et al. Beneficial effects of coronary venous retroinfusion but not left atrial administration of superoxide dismutase on myocardial necrosis in pigs. J Cardiovasc Pharmacol (in press).
32. Meerbaum S, Lang TW, Povshitkov M, et al. Retrograde lysis of coronary artery thrombus by coronary venous streptokinase administration. J Am Coll Cardiol 1985;1:1262–7.
33. Kordenat RK, Kenzi P, Stanley EL. A new catheter technique for producing experimental coronary thrombosis and selective visualization. Am Heart J 1972;82:360–4.
34. DeBoer LWV, Strauss HW, Kloner RA, et al. Autoradiography for measuring the ischemic myocardium at risk: effect of verapamil on infarct size after experimental coronary artery occlusion. Proc Natl Acad Sci USA 1980;77:6119–23.
35. Fishbein MC, Meerbaum S, Rit J, et al. Early phase acute myocardial infarct size quantification: validation of the triphenyl tetrazolium chloride tissue enzyme staining technique. Am Heart J 1981;101:593–600.

36. Miyazaki A, Hattori N, Tadokoro H, et al. More rapid thrombolysis with coronary venous retroinfusion of streptokinase compared with intravenous administration: an experimental study in canines. Eur Heart J 1990;11:936–44.
37. Gold HK, Fallon JT, Yasuda T, et al. Coronary thrombolysis with recombinant human tissue-type plasminogen activator. Circulation 1564; 70:700–7
38. Rydén L, Tadokoro H, Sjoquist PW, Kai S, Ervik M, Corday E. Pronounced accumulation of metoprolol in ischemic myocardial after coronary venous retroinfusion. J Cardiovasc Pharmacol 1989;15:22–8.
39. Rydén L, Tadokoro H, Sjoquist PW, et al. Pharmacokinetic analysis of coronary venous retroinfusion using metoprolol as a tracer tabsitri. Circulation 1989;80(suppl II):II-539
40. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54: 1496–508.
41. Ellis SG, Henschke CI, Sandor T, Wynne J, Braunwald E, Kloner RA. Time course of functional and biochemical recovery of myocardium salvaged by reperfusion. J Am Coll Cardiol 1983;1:1047–55.
42. Schwarzacher WA, Buda AJ, Lucchesi BR. Streptokinase thrombolysis in experimental coronary artery thrombosis: pattern of reflow and effect of a stenosis. Int J Cardiol 1984;6:615–27.
43. Hammond GL, Davies AL, Austin WG. Retrograde coronary sinus perfusion: a method of myocardial protection in the dog during left coronary artery occlusion. Ann Surg 1967;166:39–47.
44. Messmann M, Karaguezian H, Takeshi I, et al. Selective perfusion of ischemic myocardium during coronary venous retroinjection: a study of the causative role of venoarterial and venoventricular pressure gradients. J Am Coll Cardiol 1987;10:887–97.
45. Dray JK. Clinical experience with diastolic coronary venous retroperfusion. In: Meerbaum S, ed. Myocardial Perfusion, Coronary Reperfusion and Coronary Venous Retroperfusion. Darmstadt/New York: Steinkopff-Verlag/Springer-Verlag, 1990:199–207.
46. Guerci AD, Cliffo AA, DiPaula AF, Wetsfeldt ML. Intermittent coronary sinus occlusion in dogs: reduction of infarct size 10 days after reperfusion. J Am Coll Cardiol 1987;9:1075–81
47. Zalewski A, Goldberg S, Slysh S, Maroko PR. Myocardial protection via coronary sinus interventions: superior effects of arterialization compared with intermittent occlusion. Circulation 1985;71:1215–23.
48. Mohl W. The momentum of coronary sinus interventions clinically. Circulation 1988;77:6–12.
49. Mohl W, Gloger D, Mayr H, et al. Reduction of infarct size by pressure controlled intermittent coronary sinus occlusion. Am J Cardiol 1984;53: 923–30.
50. Braunwald E, Knatterud GL, Passamani ER, Robertson TL. Announcement of protocol change in the Thrombolysis in Myocardial Infarction trial (letter). J Am Coll Cardiol 1987;9:467.
51. Wappel M, Zalewski A, Savage M, Hessen S, Goldberg S, Maroko PR. Myocardial salvage after regional beta-adrenergic blockade. Am Heart J 1989;117:37–42